PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JWJ01056WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/004713	International filing date *(day/month/year)* 09.11.2004	Priority date *(day/month/year)* 10.11.2003
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant RANDOX LABORATORIES LTD. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05.09.2005	27.10.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Schmitt, C Telephone No. +49 89 2399-7351

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004713

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-13 as originally filed

   Sequence listings part of the description, Pages

   1, 2 as originally filed

   Claims, Numbers

   1-13 received on 09.09.2005 with letter of 08.09.2005

   Drawings, Sheets

   1/3-3/3 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 12, 13

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 12, 13 (all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-5, 9, 12, 13
	No:	Claims	1, 2, 6-8, 10, 11
Inventive step (IS)	Yes:	Claims	4
	No:	Claims	1-3, 5-13
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	none

2. Citations and explanations (Rule 70.7):

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Reference is made to the following documents:

D1: DATABASE Geneseq [Online] 18 December 2003 (2003-12-18), "Human novel cDNA sequence, SEQ ID NO:595." XP002316183 retrieved from EBI accession no. GSN:ADC30513 Database accession no. ADC30513.

D2: DATABASE Geneseq [Online] 18 December 2003 (2003-12-18), "Human novel polypeptide sequence, SEQ ID NO:1566." XP002316184 retrieved from EBI accession no. GSP:ADC31484 Database accession no. ADC31484.

D3: DATABASE EMBL [Online] 3 December 1999 (1999-12-03), "Homo sapiens genomic DNA, chromosome 11 clone:RP11-876F8, complete sequence." XP002316185 retrieved from EBI accession no. EM_HUM:AP000795 Database accession no. AP000795.

D4: WO 02/055988 A (EOS BIOTECHNOLOGY, INC) 18 July 2002.

D5: WO03/029271 A (HYSEQ, INC.) 10 April 2003.

D6: US 2003/144232 A1 (AGAMI REUVEN ET AL) 31 July 2003 (2003-07-31)

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 12 and 13 have only been partially searched due to a lack of clarity of said claims.

Claim 12 relates to the use of a second polynucleotide in the manufacture of a medicament for the treatment of cancer, in particular breast cancer. Said second polynucleotide is only defined in terms of its function namely that it hybridises with or inhibits the expression of an endogenous gene that comprises the polynucleotide of SEQ ID NO: 1 or 2.

The functional features used to defined said second polynucleotide however do not

allow to deduce the structural feature(s) characterizing said second polynucleotide, i.e. nucleotide sequence, so that the exact second polynucleotide remains unclear. In particular, due to the wording of claim 12 (i.e. a gene comprising the polynucleotide of SEQ ID NO: 1 or 2), the exact sequence of the gene comprising SEQ ID NO: 1 or 2 remains unclear, thus leaving the second polynucleotide, that hybridises with or inhibits the expression of said gene, unclear/undefined. This unclear second polynucleotide leaves therefore doubts as to the subject-matter encompassed by claim 12. Claim 12 lacks therefore clarity in the meaning of Article 6 PCT. This lack of clarity was such as to render a meaningful search over the whole claimed scope impossible.
In view of the description (page 5, lines 25-30), the search of claim 12 has been limited to the use of small interfering RNAs (i.e. siRNAs) that target the nucleic acid of sequence of SEQ ID NO: 2 or SEQ ID NO: 1, in the manufacture of a medicament for the treatment of cancer, in particular breast cancer.
The search of claim 13 has been limited accordingly.

As claims, or parts of claims, relating to subject-matter in respect to which no international search has been performed need not to be the subject of an international preliminary examination (Rule 66.1(e) PCT), an opinion of the international preliminary examining authority will only be given with respect to the subject-matter of the claims that was searched.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Document D3 discloses a clone from chromosome 11 of 76999 nucleotides wherein the sequence encompassed by nucleotide position 44950 to nucleotide position 45150 is 100% identical to SEQ ID NO: 2 of the present application.
Such clone being considered as an isolated polynucleotide comprising SEQ ID NO: 2; the subject-matter of claims 6 and 7 is considered to be anticipated by the disclosure of document D3.
Claims 6 and 7 are therefore not new in the sense of Article 33(2) PCT.

2. Document D5 (the references in parentheses applying to this document) discloses an isolated polynucleotide comprising the nucleotide sequence of SEQ ID NO: 595, an isolated peptide comprising the amino acid sequence of SEQ ID NO: 1566 and an antibody directed against a polypeptide encoded by the polynucleotide of SEQ ID NO: 595 (i.e. peptide of SEQ ID NO: 1566) (claims 1, 10, 12 and 22 and see also documents D1 and D2 for information on the sequences SEQ ID NO: 595 and SEQ ID NO: 1566 disclosed in document D5). The sequence of SEQ ID NO: 595 overlaps with the sequence of SEQ ID NO:1 and SEQ ID NO:2 of the present application over 212 and 146 nucleotides, respectively. The amino-acid sequence of SEQ ID NO: 1566 is 100% identical to the amino-acid sequence of SEQ ID NO:3 of the present application.

Claims 6, 10 and 11 are therefore not new in the sense of Article 33(2) PCT.

3. Furthermore, document D5 discloses that detection of the presence or amount of the above cited polynucleotide or polypeptide is useful for diagnosis and/or prognosis of cancer (page 4, lines 13-16, page 5, lines 20-24, page 6, line 29-page 7, line 16 and page 61, lines 5-13). In particular, the presence or increased expression of such a polynucleotide/polypeptide indicates a risk of cancer, a precancerous condition, or an ongoing malignancy.

In view of the arguments provided by the applicant, it is noted that document D5 discloses 971 polynucleotides sequences that are useful for diagnosis and/or prognosis of cancer. However, it is questionable if all of said polynucleotides sequences are useful for prognosis/diagnosis of cancer as there is no support that any of said polynucleotides or polypeptides encoded by said polynucleotides is useful for the detection of the presence of or the risk of cancer in a patient. In particular, there is no support that the polynucleotide of SEQ ID NO: 595 and /or the polypeptide of SEQ ID NO: 1566 can indeed be used for diagnosis and/or prognosis of cancer, in particular breast cancer.

On examination of the description of the present application, it can be observed that SEQ ID NO: 1, 2 or 3 is useful in the detection of the presence of or risk of **breast cancer** (see example). However, the present application fails to provided any

data/support showing that SEQ ID NO: 1, 2 or 3 are useful in the detection of the presence of or risk of any other type/kind of cancer.
Thus, the actual contribution to the state of the art (i.e. document D5) by the disclosure of the present application essentially consists of providing experimental support that SEQ ID NO: 1, 2 or 3 are useful in the detection of the presence of or risk of breast cancer.
Apart from breast cancer, the skilled person is essentially instructed by independent claim 1 to assess the presence of or the risk of cancer by detecting the presence or expression of the gene of SEQ ID NO: 1 such as disclosed in document D5. It is therefore considered that, apart from breast cancer, the present application does not differ from the disclosure of document D5.

Claims 1, 2 and 8 are therefore not new in the sense of Article 33(2) PCT.

4. Document D5, in addition, discloses that inhibitors of the biological activity of the above cited polypeptide can be administered to treat cancer (page 8, lines 3-7 and page 61, line 14-page 62, line 7).

Claims 12-13 differs from the disclosure of document D5 in that siRNAs targeting SEQ ID NO:1 or SEQ ID NO: 2 are used to treat cancer.

Claims 12-13 are therefore new in the sense of Article 33(2) PCT.

Said claims are however not considered inventive in the sense of Article 33(3) PCT. The use of siRNAs as inhibitors of the expression of a gene in the manufacture of a medicament to treat cancer is well known in the art (see document D6). Therefore, using specifically siRNAs as inhibitors of the expression of the gene of SEQ ID NO: 595 to treat cancer is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill.

Claims 12 and 13 are therefore not considered inventive in the sense of Article 33(3) PCT.

It is pointed out that a claim limited to the use of siRNAs targeting SEQ ID NO:1 or SEQ ID NO: 2 in the manufacture of a medicament for the treatment of breast cancer would be considered inventive over the prior art (see also point 6, *infra*).

5. Claims 3, 5 and 9 appear to be new in the sense of Article 33(2) PCT as their features are not disclosed in any available prior art. Said claims are however not considered inventive in the sense of article 33(3) PCT.

Claim 5, which is dependent on independent claim 1, is not considered inventive because detecting the presence of a particular gene by PCR represents standard methodology in the art.

Furthermore, in view of document D5 which refers in general terms to diagnosis and therapy of (breast) cancer (see item 3. above and page 61, lines 5-23 of document D5), the additional features set out in claim 3 which are dependent on claim 1, and in claim 9 which is dependent on claim 8 are considered obvious.

6. Document D4 (the references in parentheses applying to this document) discloses a method for diagnosing breast cancer based on the expression level a gene encoding BCO2 (claim 7).

Claim 4 differs from the disclosure of document D4 in that it is the expression or presence of the gene of SEQ ID NO: 1 which is used to diagnose breast cancer.

Claim 4 is therefore new (Article 33(2) PCT).

In view of document D4, which is considered as the closest prior art relevant to claim 4, the problem to be solved by the present application may be seen as the provision of an alternative method for diagnosing (i.e detection of the presence or the risk of) breast cancer.

Claim 4 is considered inventive in the sense of Article 33(3) PCT as none of the available prior art indicates or fairly suggests that the polynucleotide of SEQ ID NO: 1 can be used for the detection of the presence of or the risk of breast cancer in an

obvious way.

Furthermore, the disclosure of document D5 indicating that the polynucleotide of SEQ ID NO: 595 is useful for diagnosis/prognosis of breast cancer is not seen as an enabling disclosure that, in the absence of experimental data, said sequence could indeed be used in the diagnosis of breast cancer, in particular as it is questionable if all of the 971 polynucleotides sequences disclosed in document D5 are useful for prognosis/diagnosis of cancer. Furthermore, the present Authority considers that the skilled person would have had no reasonable expectation of success with SEQ ID NO: 1 due to the merely speculative assumption that SEQ ID NO: 595 could be useful for diagnosis of breast cancer.